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37 C.F.R. § 1.8

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April 5, 2007 — Charles P. Landrum
Date

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Richard C. Conrad	Group Art Unit: 1651
Serial No.: 10/667,126	Examiner: Kim, Taeyoon
Filed: September 19, 2003	Atty. Dkt. No.: AMBI:086US
For: METHODS AND COMPOSITIONS FOR ISOLATING SMALL RNA MOLECULES	Confirmation No.: 7162

PETITION TO DIRECTOR UNDER 1.181 FOR RECONSIDERATION OF RESTRICTION REQUIREMENT UNDER 37 C.F.R. §1.144

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Petition is submitted in response to the decision provided in the Office Action mailed on January 5, 2007 regarding the restriction requirement advanced on September 28, 2006 in the above-captioned application. Should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to this document, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski Deposit Account No. 50-1212/AMBI:086US/MBW.

Applicants respectfully petition the withdrawal of the restriction requirement and request rejoinder of claims 1-57 because the pending claims do not present an undue search burden on the Examiner, and the Examiner has not provided sufficient evidence of such a burden.

An Office Action was mailed on September 28, 2006, restricting originally filed claims 1-53 into six groups. Group I, claims 1-41, drawn to a method of isolating small RNA molecules; Group II, claims 42-45, drawn to methods of isolating miRNA and siRNA; Group III, claims 46 and 47, drawn to methods of isolating miRNA; and Group IV, claim 48, drawn to methods of isolating small RNA; Group V , claim 49 , drawn to a kit for isolating small RNA; and Group VI, claims 50-53, drawn to methods of isolating small RNA. In the Response mailed November 28, 2006, Applicants elected to prosecute, with traverse, claims 42-45, *i.e.*, Group II and added new claims 54-57. In the Office Action mailed on January 5, 2007, the Examiner reconsidered the restriction requirement based on Applicants' traversal and maintained the restriction with the exception of Group III claims 46 and 47, withdrawing claims 1-41, 48-53, 56 and 57 as directed to non-elected subject matter.

A. Group II Was Provisionally Elected

In response to the Restriction Requirement mailed September 28, 2006, requiring restriction of the present claims, Applicants elected the Group II (claims 42-45) with traverse. Applicants respectfully petition the withdrawal of the restriction requirement and request the rejoinder of claims 1-57 because the pending claims do not present an undue search burden on the Examiner and the Examiner has not provided sufficient evidence of such a burden.

B. Groups I, II, III, IV, and VI

The Examiner contends that Groups I, II, III, IV, and VI are distinct, each from the others because the inventions as claimed are not connected in at least one of design, operation, or effect and wherein at least one invention is patentable over the other. The Action alleges that the

methods claimed are "distinct from one another because they recite different and distinct steps which lead to different and distinct products." The Examiner supports this position by stating that "the method of Group II invention does[sic] not have a step for lysis or use; the method of Group III invention does not have a step for lysis of cells" and that "the methods of Group I and Group IV invention have different concentration[s] of guanidinium and alcohol in the steps." The Examiner has not established a basis for asserting that the claims of Groups I, II, III, IV, or VI present an undue burden.

The MPEP indicates that a restriction is proper if (1) the inventions are independent or distinct AND (2) there is a serious burden on the examiner. MPEP §803. In addition, the MPEP states that a *prima facie* case of undue burden can be shown if the Examiner shows by appropriate explanation one of the following: (A) Separate classification, (B) A separate status in the art when they are classifiable together, and (C) A different field of search. Furthermore, MPEP §808.02 states:

> Where, however, the classification is the same and the field of search is the same and there is no clear indication of separate future classification and field of search, no reasons exist for dividing among independent or related inventions. (emphasis added)

In this case, the Examiner does not establish that a serious or undue burden exists. In particular, there has been no showing of separate classification and no clear indication of separate status in the art or of a different field of search. Reversal of the restriction and examination of claims 1-57 is respectfully requested.

1. **All claim groups are class 536, subclass 25.4**

Each of the Groups (I-VI) are classified in class 536, subclass 25.4, therefore the subject matter of each group is not in a separate classification or sub-classification (page 2 of the Action dated September 28, 2007).

2. **No showing of separate status in the art or undue burden**

The various limitations in the claims of Group I, II, III, IV, or VI do not establish that each Group has a separate status in the art. Furthermore, an undue burden is not imposed upon the Examiner in searching the similar elements of Groups I, II, III, IV, and VI. The Examiner provides little explanation establishing the separate status of each claim grouping and in establishing an undue burden on the Examiner. In establishing the separate status of the claim groupings and the undue burden of searching all claims, the Examiner relies on the generic statements on page 3 of the Action that read "The several inventions above are independent and distinct, each from the other. They have acquired a separate status in the art as a separate subject for inventive effect and require independent searches. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. . .". Such a conclusory statement does not provide any explanation or basis as to why the particular claims at issue have a separate status in the art or would pose an undue burden on the Examiner.

Applicants submit that the claims of Groups I, II, III, IV, and VI are directed generally to the isolation of small RNA, which includes miRNA and siRNA, and contain similar steps for the isolation of small RNAs. For instance, claim 1 reads:

> A method for isolating small RNA molecules from cells comprising:
> a) lysing the cells with a lysing solution to produce a lysate;
> b) adding an alcohol solution to the lysate;
> c) applying the lysate to a solid support;
> d) eluting small RNA molecules from the solid support; and,

e) using or characterizing the small RNA molecules.

Claim 42 of Group II contains steps similar to steps b, c, and e of claim 1. Claim 42 reads (steps similar to claim 1 in bold):

> A method for isolating miRNA or siRNA from a sample comprising:
> a) obtaining a sample having miRNA or siRNA;
> **b) adding an alcohol solution to the sample;**
> c) adding an extraction solution to the sample;
> **d) applying the sample to a mineral or polymer support; and**
> **e) eluting the siRNA or miRNA from the mineral or polymer support.**

Furthermore, step a of claim 42 is similar to dependent claim 2 (". . . wherein the small RNA molecules include miRNA, siRNA . . ." and step c of claim 42 is similar to dependent claim 15 (". . . further comprising extracting small RNA molecules. . ."). Thus, a search of Group I would be coextensive with a search of Group II.

Claim 46 of Group III contains steps similar to steps b, c, d, and e of claim 1. Claim 46 reads (steps similar to claim 1 in bold):

> A method for isolating miRNA molecules from a sample comprising:
> **a) adding an alcohol solution to the sample;**
> **b) applying the sample to a mineral or polymer support;**
> **c) eluting miRNA molecules from the support; and**
> **d) using or characterizing the miRNA molecules.**

A search of Group I would be coextensive with a search of Group III.

Claim 48 of Group IV contains steps similar to steps a, b, c, d, and e of claim 1. Claim 48 reads (steps similar to claim 1 in bold):

> A method for isolating small RNA molecules from a sample comprising:
> **a) lysing cells in the sample with a lysing solution comprising guanidinium, wherein a lysate with a concentration of at least about 1 M guanidinium is produced;**

b) extracting small RNA molecules from the lysate with an extraction solution comprising phenol;
c) adding to the lysate an alcohol solution for form a lysate/alcohol mixture, wherein the concentration of alcohol in the mixture is between about 35% to about 70%;
d) applying the lysate/alcohol mixture to a mineral or polymer support;
e) eluting the small RNA molecules from the mineral or polymer support;
f) capturing the small RNA molecules; and
g) using the isolated small RNA molecules.

Furthermore, step b of claim 48 is similar to dependent claim 15 of Group I (". . . further comprising extracting small RNA molecules. . .") and step f of claim 48 is similar to dependent claim 35 of Group I (". . . further comprising capturing the eluted small RNA molecules."). Thus, a search of Group I would be coextensive with a search of Group IV.

Claim 50 of Group VI contains steps similar to steps a, b, c, and d of claim 1. Claim 50 reads (steps similar to claim 1 in bold):

A method for isolating small RNA molecules from a sample comprising:
a) lysing cells in a lysing solution to produce a lysate;
b) extracting small RNA molecules from the lysate with an extraction solution comprising phenol;
c) adding to the lysate an alcohol solution to form a lysate/alcohol mixture;
d) applying the lysate/alcohol mixture to a first solid support;
e) collecting flow-through lysate/alcohol mixture;
f) adding to the flow-through lysate/alcohol mixture an alcohol solution;
g) applying the lysate/alcohol mixture to a second solid support; and
h) eluting small RNA molecules from the solid support.

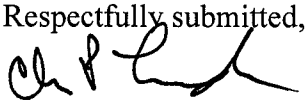
Furthermore, step b of claim 50 is similar to dependent claim 16 of Group I (". . . wherein the extraction solution comprises phenol. . ."). Thus, a search of Group I would be coextensive with a search of Group VI.

In traversing the restriction requirement on the grounds set forth above, Applicants specifically take no position with regard to whether any sets of the present claims or any individual present claim are or are not patentably distinct from any other set of claims or individual claim. Rather, Applicants argue without acquiescence that, under the circumstances of this case and in view of the applicable rules and statements of the MPEP, the stated restriction is not proper, whether those claims are patentably distinct or not. Such arguments do not create an estoppel against Applicants and are not an admission that the restricted Groups are either patentably distinct or patentably indistinct from one another.

In conclusion, each of the claim groupings are directed to similar and overlapping methods of varying scope, as demonstrated by claims dependent from, either directly or indirectly, claim 1 of Group I. There must be a serious burden on the examiner (MPEP §808.02). The Examiner does not establish that such a burden exists. For the reasons provided above, Applicants respectfully request the reversal of the restriction and request examination of all claims in Groups I, II, III, IV, and VI.

Therefore, applicants respectfully petition the Commissioner to overturn the restriction of claims 1-57. Should any questions regarding this paper arise, the interested party should contact the undersigned at 512-536-3167.

Respectfully submitted,



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Date: April 5, 2007

APPENDIX A – CLEAN COPY OF PENDING CLAIMS

1. (withdrawn) A method for isolating small RNA molecules from cells comprising:

a) lysing the cells with a lysing solution to produce a lysate;
b) adding an alcohol solution to the lysate;
c) applying the lysate to a solid support;
d) eluting small RNA molecules from the solid support; and,
e) using or characterizing the small RNA molecules.

2. (withdrawn) The method of claim 1, wherein the small RNA molecules include miRNA, siRNA, snRNA, snoRNA, tRNA molecules, or combinations thereof.

3. (withdrawn) The method of claim 2, wherein the small RNA molecules are miRNA molecules.

4. (withdrawn) The method of claim 1, wherein at least 20% of the small RNA molecules from the cells are isolated.

5. (withdrawn) The method of claim 4, wherein at least 50% of the small RNA molecules from the cells are isolated.

6. (withdrawn) The method of claim 1, wherein the lysing solution comprises a chaotropic agent or detergent.

7. (withdrawn) The method of claim 6, wherein the lysing solution comprises a chaotropic agent.

8. (withdrawn) The method of claim 7, wherein the concentration of the chaotropic agent in the lysing solution is at least about 2.0 M.

9. (withdrawn) The method of claim 7, wherein the lysing solution comprises guanidinium.

10. (withdrawn) The method of claim 9, wherein the concentration of guanidinium is at least about 2.0 M.

11. (withdrawn) The method of claim 10, wherein the lysing solution further comprises a detergent and a buffer.

12. (withdrawn) The method of claim 11, wherein the concentration of the detergent is about 0.1% to about 2%.

13. (withdrawn) The method of claim 12, wherein the detergent is N-lauroyl sarcosine.

14. (withdrawn) The method of claim 11, wherein the concentration of the buffer is about 10 mM to about 300 mM.

15. (withdrawn) The method of claim 1, further comprising extracting small RNA molecules from the lysate with an extraction solution comprising an organic solvent prior to applying the lysate to the solid support.

16. (withdrawn) The method of claim 15, wherein the extraction solution comprises phenol.

17. (withdrawn) The method of claim 16, wherein the extraction solution further comprises chloroform.

18. (withdrawn) The method of claim 1, wherein the amount of alcohol solution added to the lysate makes the lysate about 20% to about 70% alcohol.

19. (withdrawn) The method of claim 18, wherein the amount of alcohol solution added to the lysate makes the lysate about 50% to 60% alcohol.

20. (withdrawn) The method of claim 18, wherein the alcohol solution is added to the lysate before extraction with an organic solvent.

21. (withdrawn) The method of claim 1, further comprising washing the solid support with a first wash solution after applying the lysate to the solid support.

22. (withdrawn) The method of claim 21, wherein the first wash solution comprises a chaotropic agent.

23. (withdrawn) The method of claim 22, wherein the chaotropic agent is guanidinium and the first wash solution further comprises alcohol.

24. (withdrawn) The method of claim 21, further comprising washing the solid support with a second wash solution after washing with the first wash solution.

25. (withdrawn) The method of claim 24, wherein the second wash solution comprises alcohol.

26. (withdrawn) The method of claim 1, wherein the small RNA molecules are eluted from the solid support at a temperature of about 60 °C to about 100 °C.

27. (withdrawn) The method of claim 1, wherein the small RNA molecules are eluted from the solid support with a low-ionic-strength solution.

28. (withdrawn) The method of claim 27, wherein the ionic solution comprises up to 10 mM salt.

29. (withdrawn) The method of claim 1, wherein the solid support is a mineral support or polymer support.

30. (withdrawn) The method of claim 29, wherein the mineral support or polymer support is a column comprising silica.

31. (withdrawn) The method of claim 29, wherein the mineral or polymer support is a set of beads made of an absorptive polymer.

32. (withdrawn) The method of claim 31, wherein the set of beads are collected by centrifugation, filtration, or magnetic capture.

33. (withdrawn) The method of claim 30, wherein the silica is glass fiber.

34. (withdrawn) The method of claim 1, further comprising passing the lysate through the column by centrifugation or gas pressure.

35. (withdrawn) The method of claim 1, further comprising capturing the eluted small RNA molecules.

36. (withdrawn) The method of claim 33, wherein the eluted small RNA molecules are captured on a filter and then collected.

37. (withdrawn) The method of claim 1, wherein the small RNA molecules are single stranded.

38. (withdrawn) The method of claim 1, wherein the small RNA molecules are double stranded.

39. (withdrawn) The method of claim 1, wherein the small RNA molecules have at most 100 nucleotides or fewer.

40. (withdrawn) The method of claim 39, wherein the small RNA molecules have at most 70 nucleotides or fewer.

41. (withdrawn) The method of claim 40, wherein the small RNA molecules have at most 30 nucleotides or fewer.

42. (currently amended) A method for isolating miRNA or siRNA from a sample comprising:

a) obtaining a sample having miRNA or siRNA;
b) adding an alcohol solution to the sample <u>to an alcohol concentration of about 35% to about 70%</u>;
c) adding an extraction solution to the sample;
d) applying the sample to a mineral or polymer support; and
e) eluting the siRNA or miRNA from the mineral or polymer support <u>to form eluted siRNA or miRNA</u>.

43. (original) The method of claim 42, wherein the sample is a cell lysate.

44. (original) The method of claim 43, wherein the cell lysate is produced by adding a lysing solution comprising a chaotropic agent or detergent to cells having miRNA or siRNA.

45. (currently amended) The method of claim 42, wherein the eluted siRNA or miRNA ~~sample~~ is enriched at least about 10-fold by mass for miRNA or siRNA.

46. (currently amended) A method for isolating miRNA molecules from a sample comprising:

a) adding an alcohol solution to the sample to an alcohol concentration of about 35% to about 70%;
b) applying the sample to a mineral or polymer support;
c) eluting miRNA molecules from the support; and
d) using or characterizing the miRNA molecules.

47. (original) The method of claim 46, wherein the sample is a cell lysate.

48. (withdrawn) A method for isolating small RNA molecules from a sample comprising:

a) lysing cells in the sample with a lysing solution comprising guanidinium, wherein a lysate with a concentration of at least about 1 M guanidinium is produced;
b) extracting small RNA molecules from the lysate with an extraction solution comprising phenol;
c) adding to the lysate an alcohol solution for form a lysate/alcohol mixture, wherein the concentration of alcohol in the mixture is between about 35% to about 70%;
d) applying the lysate/alcohol mixture to a mineral or polymer support;
e) eluting the small RNA molecules from the mineral or polymer support;
f) capturing the small RNA molecules; and
g) using the isolated small RNA molecules.

49. (cancelled)

50. (withdrawn) A method for isolating small RNA molecules from a sample comprising:

a) lysing cells in a lysing solution to produce a lysate;

b) extracting small RNA molecules from the lysate with an extraction solution comprising phenol;

c) adding to the lysate an alcohol solution to form a lysate/alcohol mixture;

d) applying the lysate/alcohol mixture to a first solid support;

e) collecting flow-through lysate/alcohol mixture;

f) adding to the flow-through lysate/alcohol mixture an alcohol solution;

g) applying the lysate/alcohol mixture to a second solid support; and

h) eluting small RNA molecules from the solid support.

51. (withdrawn) The method of claim 50, wherein the lysate/alcohol mixture applied to the first solid support is between about 20% to about 35% alcohol.

52. (withdrawn) The method of claim 50, wherein the lysate/alcohol mixture applied to the second solid support is between about 35% to about 70% alcohol.

53. (withdrawn) The method of claim 50, further comprising using or characterizing the small RNA molecules.

54. (previously presented) The method of claim 42, wherein elution is with an ionic solution.

55. (previously presented) The method of claim 46, wherein elution is with an ionic solution.

56. (withdrawn) The method of claim 48, wherein elution is with an ionic solution.

57. (withdrawn) The method of claim 50, wherein elution is with an ionic solution.

58. (new) The method of claim 46, further comprising washing the mineral or polymer support with a first wash solution after applying the sample to the mineral or polymer support.

59. (new) The method of claim 58, wherein the first wash solution comprises a chaotropic agent.

60. (new) The method of claim 59, wherein the chaotropic agent comprises guanidinium and the first wash solution further comprises alcohol.

61. (new) The method of claim 59, further comprising washing the mineral or polymer support with a second wash solution.

62. (new) The method of claim 61, wherein the second wash solution comprises alcohol.

63. (new) The method of claim 60, wherein the guanidinium is in the form of guanidinium isocyanate, the first wash solution comprises ethanol at 70%, and the second wash solution comprises ethanol at 80%.

64. (new) A method for isolating small RNA molecules from a sample comprising:

a) adding an ethanol solution to the sample to result in an ethanol concentration of between about 35% to about 70%;
b) applying the sample to a mineral support;
c) eluting small RNA molecules from the support; and
d) using or characterizing the small RNA molecules.

65. (new) The method of claim 64, wherein the small RNA molecules comprise miRNA molecules.

66. (new) The method of claim 64, wherein the small RNA molecules comprise siRNA molecules.

67. (new) The method of claim 64, further comprising washing the mineral support with a first wash solution after applying the sample to the mineral support.

68. (new) The method of claim 67, wherein the first wash solution comprises a chaotropic agent.

69. (new) The method of claim 68, wherein the chaotropic agent comprises guanidinium and the first wash solution further comprises alcohol.

70. (new) The method of claim 69, further comprising washing the mineral support with a second wash solution.

71. (new) The method of claim 70, wherein the second wash solution comprises alcohol.

72. (new) The method of claim 70, wherein the guanidinium is in the form of guanidinium isocyanate at a concentration of 1.6 M, the first wash solution comprises ethanol at 70%, and the second wash solution comprises ethanol at 80%.